About the cost of opposing the Goumarin-inhibitor theory

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About the Cost of Opposing the Coumarin-Inhibitor Theory – Reply

Dear Sir,

At this moment it is common knowledge that vitamin K takes part in an enzymatic carboxylation that causes a postribosomal modification of several proteins in several organs. The best known proteins are the coagulation factors II, VII, IX, X and protein C, produced in the liver and shed out in the plasma. It also is known to everybody familiar with the field that in certain species (man, cow) vitamin K deficiency or administration of coumarin congeners will cause the uncarboxylated factors to circulate whereas in other species (rat, rabbit, chicken!) no such uncarboxylated proteins have been demonstrated in the plasma although they do pile up in the liver.

The question Dr. Girolami is interested in is whether or not one of these acarboxyfactors does inhibit the Thrombotest time. This is a question of particular interest to me as we reported this inhibition for the first time in 1963. We recognised it on basis of the disproportionally long Thrombotest times of undiluted anticoagulated plasma (the PIVKA phenomenon).

On basis of these findings we were the first to postulate that vitamin K would act at a postribosomal level and that abnormal factors would circulate in man under conditions of vitamin K deficiency or the intake of coumarin derivatives. At this moment I do not feel that my early observations are mistaken. Not because they led to a hypothesis that proved to be fruitful as a basis for further research and until now goes unchallenged but rather because they have been repeated and confirmed numerous times in other laboratories as well as in our own. I am completely aware of the fact that this implies that I have reasons not to accept the evidence brought forward by Dr. Girolami. (To cite one example: it is unacceptable to use as evidence against the PIVKA inhibition the absence of coumarin induced inhibition in the chicken if it is known that in this species the uncarboxylated factors are not demonstrated in the plasma). If I, like Dr. Girolami, would be unable to repeat the experiments from another lab, I would be reluctant to use words like fraud and dishonesty.

I would prefer to try and repeat, confirm or falsify the original results in a joint venture and thus arrive at a common opinion between the two of us before trying to convince the rest of the world.

Completely unrelated to the main question but frequently appearing as a confounding issue is the problem of the importance of "inhibition sensitivity" of the thromboplastins. In our experience such differences do exist. They are at the basis of the fact that the "percentage of coagulation activity" obtained with different thromboplastins may differ considerably. Thrombotest appears to be especially sensitive as witnessed by the well-known fact that e.g. "10% Thrombotest" is found with the vitamin K dependent factors at levels of around 20% etc. The practical importance of this fact is that it makes comparison of thromboplastins difficult. Nobody has ever shown that the PIVKA-phenomenon is of any clinical importance and I agree with Dr. Girolami that inhibitor sensitivity cannot be used as an argument in favour of one type of thromboplastin over the other. With the permission of the editor I will end this discussion with a personal note.

I believe that the personal involvement of researchers is the spice in science. I also believe that any spice added in excess makes any dish unpalatable. I fear that Dr. Girolami, in adding his favorite flavour to this discussion, has gone as far as the limits of good taste allow.

I feel that the only step that can be taken from here on is to invite Dr. Girolami to my lab and I do hope that the next paper on this subject will be signed by him and me together no matter whether it refutes or reconfirms my original observations.

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